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Abstract

The current understanding of cadmium impacts to avian species has been improved by recent studies and the extensive literature review completed during the development of the U.S. Environmental Protection Agency Ecological Soil Screening Levels (Eco-SSLs). Therefore, we sought to update the cadmium toxicity reference value (TRV) for birds used by regulatory agencies and resource trustees in California for predictive ecological risk assessments. We surveyed the available secondary and primary literature sources to identify the lowest, ecologically relevant no observable adverse effect levels (NOAELs) for oral exposure of birds to cadmium. Review focused on evaluating TRVs between the currently used TRV (0.08 mg/kg/d) and the Eco-SSL TRV (1.47 mg/kg/d), considering the application of an updated ingestion rate model (Nagy *et al*., 2001) and uncertainty factors. After consideration of the endpoints and evaluation of the experimental results, we propose an ecologically protective NOAEL TRV of 0.7 mg/kg/d, based primarily on the kidney toxicity data in wood ducks (Mayack *et al*., 1981), but supported by other studies that indicate the kidney is a critical target organ for cadmium toxicity. This TRV is also protective of reproductive effects (Leach *et al*., 1979), another sensitive endpoint for cadmium toxicity. In addition, a lowest observable adverse effect level (LOAEL) of 1.0 mg/kg/d was identified based on kidney nephrosis in mallards (Cain *et al*., 1983). Overall, these updated TRVs incorporate more recent studies and reviews on cadmium toxicity in birds while establishing thresholds based on ecologically relevant endpoints.

BACKGROUND

Assessing ecological risk to mammals and birds from contaminants involves a comparison of exposure levels as daily doses to an appropriate TRV. A TRV is the daily dose of a chemical in units of mg chemical per kg wet body weight per day (mg/kg BW/d) that elicits a particular biological effect, such as behavioral abnormality, reproductive failure, or altered weight gain. For a given study and endpoint, the lowest, statistically significant adverse effect is the LOAEL and the next lowest dose is the NOAEL. The daily dose for an organism at a given site is estimated using a food-chain

model that incorporates exposure across all possibly complete pathways including, but not limited to, ingestion of prey, surface water, and incidental soil/sediment.

In a cooperative effort begun in 1995, the U.S. Department of the Navy and the U.S. Environmental Protection Agency (USEPA) Region 9 Biological Technical Assistance Group (BTAG) developed mammalian and avian TRVs for a number of inorganic and organic chemicals of concern at military facilities in California [Engineering Field Activity West (EFA West), 1997]. The Navy/BTAG TRV Workgroup selected biological effects that primarily related to growth, reproduction, and development; however, all effects deemed ecologically relevant were considered when developing TRVs. TRVs were developed to represent the most sensitive, ecologically relevant NOAELs (TRV-Low) and mid-range adverse effect levels (TRV-High) across all available endpoints, studies, and species. An estimated daily dose below a TRV-low suggests little or no potential risk whereas exceedance of a TRV-high indicates a significant immediate risk (EFA West, 1997). The TRVs were selected from the published literature via consensus among the Navy, Navy consultants, and several regulatory agency representatives within the BTAG, including the USEPA, Department of Toxic Substances Control, Human and Ecological Risk Division (DTSC-HERD), Regional Water Quality Control Board (RWQCB), Office of Environmental Health Hazard Assessment (OEHHA), National Oceanic and Atmospheric Administration (NOAA), U.S. Fish and Wildlife Service (USFWS), and the California Department of Fish and Game, Office of Spill Prevention and Response (DFG-OSPR).

In the interim final TRV document released in 1997, the TRV Workgroup supported the adoption of an avian cadmium TRV-Low of 0.08 mg/kg BW/day. This NOAEL was derived by applying an uncertainty factor of 10 to an unbounded LOAEL (0.8 mg/kg BW/d; Cain *et al*., 1983) for kidney degeneration in mallards. The Cain *et al. (*1983) study was selected over other studies because the mallard was considered to be a sensitive species and the kidney was a known target organ for cadmium toxicity. The TRV-high as a mid-range adverse effect level was established at 10.43 mg/kg BW/d based on decreased body weight and testes weight in Japanese quail exposed to cadmium chloride (Richardson and Spivey-Fox, 1974). This dose was in the mid-range of reproductive effects and associated with changes in body, liver, and kidney weights.

THE ECO-SSL CADMIUM TRV FOR BIRDS AND RATIONALE FOR A REVISED TRV

The current understanding of cadmium impacts to avian species has been improved by recent studies, scholarly reviews on cadmium effects on wildlife (e.g., Burger, 2008), and the extensive literature review completed during the development of the USEPA's Eco-SSLs (USEPA, 2005). The cadmium Eco-SSL (1.47 mg/kg BW/day; USEPA, 2005) for birds was derived using a TRV that was the geometric mean of NOAEL values for reproduction and growth. This value was determined to be lower than the lowest bounded LOAEL for reproduction, growth, and survival (2.37 mg/kg BW/d; USEPA, 2005). BTAG members other than USEPA do not concur with some of the methodology used to develop this Eco-SSL, such as limiting the selection of a TRV-Low to reproduction, growth and mortality endpoints; calculating a geometric mean TRV based

on different endpoints, studies, and species; and excluding unbounded LOAELs. BTAG members other than USEPA recommend that all ecologically relevant endpoints (e.g., behavioral, pathological, and systemic effects) be considered in TRV development, in as much as these endpoints could potentially affect the survival and reproductive fitness of an organism. Use of the geometric mean should be restricted to toxicity data that are representative of a population of similar studies (e.g., equivalent species, exposure duration, and endpoints). In addition, unbounded LOAELs provide valuable information about the toxicity of a chemical, as in the Cain *et al*. (1983) study on cadmium, and should be considered in TRV development. However, all BTAG members are in agreement that deriving NOAELs from LOAELs with an uncertainty factor, as with the original avian TRV-low for cadmium, introduces additional uncertainty into the risk assessment. In an effort to reduce this uncertainty, BTAG decided to determine if a cadmium NOAEL could be identified directly. Accordingly, available cadmium toxicity information for birds (*i.e.*, the Eco-SSL literature review and a review of more recent studies) was re-evaluated by focusing on sensitive and ecologically relevant endpoints to update the cadmium TRV for birds used in California for predictive risk assessments. In addition, the need to establish the most sensitive, ecologically relevant LOAEL to help interpret exposures between the TRV-low and TRV-high has become apparent as well.

Following the rationale presented in the original Navy/BTAG effort to set low TRVs (EFA West, 1997), the BTAG supports using the lowest credible, ecologically relevant NOAEL from the literature. This approach is supported by Superfund guidance for ecological risk assessment (USEPA, 1997) and is protective of individuals that are potentially the most toxicologically sensitive to cadmium. While the BTAG realizes that no single study can account for differences in species susceptibility and differences in effects and absorption for various forms of cadmium, a single study can be used to represent a dose that is protective for a variety of species and toxicological endpoints (*i.e.*, protecting the most toxicologically sensitive bird species is protective of other bird species).

BTAG LITERATURE REVIEW IN SUPPORT OF REVISED AVIAN TRV FOR CADMIUM

The BTAG surveyed available primary and secondary literature sources to identify the lowest, ecologically relevant cadmium NOAELs for oral exposure of birds. Review focused on evaluating TRVs between the currently used BTAG TRV (0.08 mg/kg BW/day) and the Eco-SSL TRV (1.47 mg/kg BW/day). Studies included those from the Eco-SSL effort (Table 5.1 and Section 7.5 of the cadmium Eco-SSL) and those resulting from an independent literature review conducted by the BTAG. The BTAG review focused on studies published after the Eco-SSL review was complete (2004 to May 2008). The decision was also made to update the Eco-SSL TRVs using the more recent allometric equations for food ingestion rates by Nagy *et al. (*2001), rather than continuing to use the earlier equations by Nagy *et al. (*1987; Table 1).

BTAG representatives from DTSC-HERD and DFG-OSPR participated in the initial review of cadmium toxicity studies. Fifteen studies were reviewed for consideration in deriving a cadmium TRV-Low for birds (Tables 1 and 2; Figure 1). Preference was given to studies that orally administered cadmium in various forms over a sensitive life stage for an intermediate (greater than 14 days), or chronic (greater than 365 days) exposure period. Acute exposure studies and studies utilizing other exposure routes such as injection or gavage were not considered acceptable. Other studies were rejected based on the following: (1) conclusions were drawn using inappropriate statistics, (2) endpoints were evaluated that had questionable ecological relevance or presented difficulty in interpretation, (3) a clear dose response relationship was not demonstrated, and/or (4) it was not possible to determine the dose or form of cadmium administered. These fifteen studies evaluated cadmium effects on body weight, organ weight, tissue histology, reproduction, behavior, and blood and enzyme chemistry. These studies indicated that doses near or below 1.5 mg/kg BW/day may cause a variety of potentially adverse effects.

After due deliberation, the BTAG selected six papers (Table 2) that were deemed to represent the most relevant studies based on the following information:

- stated or estimated NOAEL or LOAEL
- experimental design
- exposure duration/frequency
- cadmium form
- exposure medium
- organism
- observed effects (including statistical interferences)
- best professional judgment concerning the value of the paper, with focus on "fatal flaws".

SUMMARY OF AVIAN CADMIUM STUDIES CONSIDERED IN TRV-LOW DEVELOPMENT

Table 2 identifies the six studies retained for in-depth review (Bokori *et al.*1996, Cain *et al*., 1983, Leach *et al*., 1979, Mayack *et al*., 1981, White and Finley, 1978, and White *et al*., 1978). The endpoints in these studies included tissue histology (Mayack *et al.,*1981, Cain *et al.,*1983, Bokori *et al.,*1996, White *et al*., 1978), body weight (Leach *et al*., 1979, Mayack *et al*., 1981, Cain *et al.*1983), reproductive effects (Leach *et al.*1979, Bokori *et al*., 1996, White and Finley, 1978, White *et al*., 1978), relative organ weight (Bokori *et al.*1996, Cain *et al.*1983, White and Finley, 1978 and White *et al*., 1978), and blood and enzyme chemistry (Cain *et al*., 1983). Of those studies, two papers (Mayack *et al*., 1981 and Leach *et al*., 1979) presented results that best supported the selection of a NOAEL based on sensitive, ecologically relevant endpoints. These studies are discussed in detail below.

Mayack *et al. (*1981) reported on the adverse effects of cadmium on kidney structure in wood ducks. One-week-old wood ducks, hatched from eggs collected from wild populations in South Carolina, were fed anhydrous cadmium chloride at levels of 0, 1,

10, and 100 mg/kg incorporated in a turkey starter ration for a period of three months. The potential effects of different protein levels were explored by incorporating either 18% or 30% protein in the diet. Seven drakes from each treatment group were sacrificed at 13 weeks of age. The remaining drakes from the 100 mg/kg (7.0 mg/kg BW/day) cadmium treatment groups were transferred to high-protein control feed and sacrificed 3 to 33 days later. Blood, liver, kidney, spleen, proventriculus, small intestine, brain, large intestine tissue with pancreas, and feathers were collected and analyzed. There were no significant differences in body weight at 13 weeks of age between any of the groups. No pathological changes were noted in the liver, spleen, proventriculus, small intestine, brain, or large intestine in any of the treatment groups. Mild to extensive vacuolation of pancreatic acinar cells and focal necrosis were observed in 75% of the birds sampled and, in general, were more severe in the higher cadmium level treatment groups. Significant kidney lesions were not observed with cadmium in the diet at 0, 1, or 10 mg/kg (0.68 mg/kg BW/day). At dietary concentrations of 100 mg/kg (7.0 mg/kg BW/day), pathological changes observed in the kidney included: tubular cell necrosis, hypertrophy of nuclei, diffuse fibrosis, calcification in some degenerated epithelial cells, presence of hyaline casts, evidence of attempted tubular regeneration (focal hyperplasia of epithelial cells), and multiple foci of lymphoid cells. The effects were more severe in the lower protein diet. Based on the significant differences in kidney histopathology described above, the estimated NOAEL and LOAEL are 0.68 and 7.0 mg/kg BW/day, respectively.

Leach et *et al*. (1979) reported on broiler chicks and laying hens fed diets supplemented with 0, 3, 12 and 48 mg/kg cadmium sulphate. Three separate experiments were conducted. In the Experiment 1, chicks were fed the experimental diets described above until six weeks of age. At bi-weekly periods, several chicks were killed and the liver, kidney, and breast muscle sampled. In the 12-week Experiment 2, 8-month old laying hens were fed the experimental diets (basal diet contained 0.07 mg cadmium/kg diet) with eggs sampled on a weekly basis and production recorded. At the end of the study, the hens were killed, and the liver and kidneys were sampled for analysis. In Experiment 3, six month-old laying hens were fed for 48 weeks as above (basal diet contained 0.22 mg cadmium/kg diet), and egg production was recorded. In Experiment 2, egg production was significantly depressed by 12 mg/kg (7% decrease; 0.75 mg/kg BW/d) and 48 mg/kg (25% decrease; 3.0 mg/kg BW/day) cadmium in the diet. In the 12-month Experiment 3, egg production and eggshell thickness were significantly decreased in the 48 mg/kg diet (40% decrease; 3.0 mg/kg BW/day). Due to the longer duration of the study, the third experiment was selected for use in developing the TRV-Low. Based on the significant differences in egg production, the estimated NOAEL and LOAEL for reproductive effects were 0.75 and 3.0 mg/kg BW/day, respectively.

These studies indicated that reproductive and renal endpoints, two sensitive targets for cadmium toxicity, were not adversely affected at daily doses of approximately 0.7 mg/kg BW/d. This threshold was consistent in two different species and included a non-domesticated species, the wood duck. Therefore, an updated TRV-low of 0.7 mg/kg BW/d was identified.

Summary of Other Studies Considered Supportive of a TRV-Low, by Toxicological Endpoint

In addition to these two studies, BTAG identified four other studies that directly or indirectly supported the development of an avian cadmium TRV-Low (Bokori *et al*., 1996, Cain *et al*., 1983, White and Finley, 1978, and White *et al*., 1978). Doses between 1 and 7 mg/kg BW/day caused effects on body weight, blood and enzyme chemistry, renal and hepatic tissue, and reproduction. Each effect is discussed in detail below by endpoint.

Body weight

Effects on body weight were observed in the majority of the studies reviewed. The lowest NOAEL for body weight was 1.0 mg/kg BW/day for both mallard ducks exposed for 12 weeks (Cain *et al*., 1983) and domestic chickens exposed for six weeks (Leach *et al*., 1979). Leach *et al*. (1979) also noted a LOAEL at 4.0 mg/kg BW/day in chickens. Chickens fed 75 mg/kg cadmium (3.2 mg/kg BW/d) in the diet from 2 to 41 weeks of age had decreased body mass compared to birds fed 25 mg/kg cadmium or the control diet (Bokori *et al*., 1996). These data indicate that a TRV-Low of 0.7 mg/kg/d would be below levels that would result in adverse effects on growth.

Some of the six primary studies reviewed showed no change in weight during the duration of the experiment (White and Finley, 1978, Mayack *et al*., 1981). Others found a wide range of responses to varying doses of cadmium. The range of LOAELs noted in the majority of the studies reviewed may have been attributable to differences in species, ages of the birds from inception to termination of the study, diets, or study lengths or other factors such as proposed by Sant'Ana *et al. (*2005). They found that male Japanese quail exposed to 100 mg/kg in diet lost weight at the end of the study of 28 days. The authors surmised there may have been a cumulative effect of cadmium accumulation which caused depletion of liver and muscular glycogen resulting in changes in energetic metabolism which could also induce a population effect (heightened susceptibility to predation). Other studies (Blalock and Hill, 1988; Jacobs *et al.*1983; Jacobs *et al.*1978; Mayack *et al.*1981; and Spivey Fox *et al.*1971) have identified substances (protein, zinc, copper, calcium, iron, and ascorbic acid) that could influence the toxicity of orally consumed cadmium and perhaps affect weight gain or loss. Jacobs *et al. (*1979) suggested that "moderate excesses of essential elements (may play a role) in decreasing absorption and retention of low dietary levels of cadmium," which could explain the adverse effects found in some studies only at the higher levels.

Blood chemistry

In a 12-week study by Cain *et al. (*1983), mallard ducklings were exposed to cadmium chloride in the diet at 0, 5, 10, or 20 mg/kg (nominal concentrations). At 8 weeks, there were significant decreases in packed cell volume and hemoglobin concentration and a significant increase in serum glutamic pyruvic transaminase (GPT) between the 20

mg/kg treatment (1.02 mg/kg BW/d) and all other groups. No other blood chemistry measurement indicated a reaction to cadmium ingestion.

White and Finley (1978) and White *et al*. (1978) conducted a study in which one-year-old mallard ducks were fed 0, 2, 20, and 200 mg/kg (nominal concentrations) of cadmium chloride in the diet for 30, 60, and 90 days of treatment. The first paper (White and Finley, 1978) reported on cadmium tissue levels, body weights, blood chemistry, and egg production. No significant differences were noted in hematocrits and hemoglobin concentrations between control birds and those fed treated food during the study. The second paper evaluated the histopathological effects of the cadmium diet (see Renal and Hepatic Effects).

Renal and Hepatic Effects

Kidney tissue usually accumulates more cadmium than liver tissue because once cadmium is absorbed, it is bound to metallothionein that is deposited in the liver, and later transported to the kidney cortex (Engstrom and Nordberg, 1979). Eventually the binding capacity of kidney metallothionein for cadmium is exceeded, and tubular dysfunction occurs (Nordberg, 1978).

Cain *et al*. (1983), in the study described above, reported mild to moderately severe kidney degeneration in four growing mallards fed 14.6 mg/kg cadmium for 12 weeks with an estimated LOAEL of 1.0 mg/kg BW/d. Ducklings fed the control diet (0.1 mg/kg) for 12 weeks did not have kidney lesions. This study was the basis for the BTAG TRV-Low (with an uncertainty factor of 10) but was not included in the Eco-SSL data set because it is an unbounded LOAEL.

Bokori *et al. (*1996) carried out a study with broiler cockerel chickens for 274 days. Cadmium sulfate was fed in diet at levels of 0, 25, and 75 mg/kg. The investigators observed pathological fatty infiltration of the liver and focal lympho-histiocytic interstitial inflammation in the kidney of birds exposed to cadmium in the diet at 25 mg/kg (1.1 mg/kg BW/d) and 75 mg/kg (3.2 mg/kg BW/d). However, changes were most severe at the 75 mg/kg dose level with larger areas of the kidney affected and fibrosis present. One chicken in the 75 mg/kg cadmium group had an adenoma originating from the kidney. These results support the view that prolonged cadmium exposure leads to the development of tissue histological changes in the kidney. Prolonged cadmium exposure in the cockerels also increased the relative mass of the liver. A NOAEL of 1.1 mg/kg BW/day and a LOAEL of 3.2 mg/kg BW/day were calculated for relative liver mass and severe kidney histopathology.

Mayack *et al*. (1981), in the study described above, also saw renal damage occurring in wood ducks at 3 months at a dietary level of 100 mg/kg (7.0 mg/kg BW/day), but not 10 mg/kg (0.68 mg/kg BW/day).

White *et al*. (1978) described a histopathologic evaluation on sections of the kidneys (this section) and testes (described in Reproductive Effects section below) of mallards. No significant pathological alterations were present in kidneys of the control ducks. In

the kidney, cadmium treatment caused degeneration of the renal tubules. In some cases, the renal damage had progressed to the stage of actual necrosis of the tubular epithelium, a response usually associated with interstitial inflammatory process. They noted a greater incidence of kidney lesions (interstitial nephritis and tubular degeneration) in birds of the 200 mg/kg group (20.0 mg/kg BW/d) in which lesions were more frequent at 60 and 90 days than at 30 days. All ten kidneys of ducks in the 200-mg/kg group showed slight to severe interstitial nephritis and tubular degeneration after 60 and 90 days. Slight to moderate tubular necrosis was evident in 7 of 10 animals in the 200 mg/kg group after 60 days, and 7 of 10 showed slight to severe alterations after 90 days. Kidney weights of the 200 mg/kg group were significantly greater after 60 and 90 days that those of the controls. Kidneys of ducks fed 2 and 20 mg/kg cadmium (1.45 mg/kg BW/d) were relatively unaffected with slight tubular degeneration was present in one bird of the 20 mg/kg group, but no tubular necrosis occurred in either group. There was no difference in liver weights among any of the treatment groups. A NOAEL of 1.45 mg/kg BW/day and a LOAEL of 20.0 mg/kg BW/day were calculated for relative liver mass and severe kidney histopathology.

Reproductive effects

Leach *et al*. (1979), in the study described above, found that dietary cadmium in chickens decreased egg production and eggshell thickness with NOAEL and LOAEL for reproductive effects at 0.75 and 3.0 mg/kg BW/d, respectively.

Bokori *et al. (*1996), in the study described above, noted adverse effects in chicken testes from cadmium exposure. Prolonged cadmium exposure of the cockerels decreased markedly the relative mass of the testes. Birds exposed to 75 mg/kg cadmium had decreased spermatogenesis and atrophy of the germinal epithelium of the testes, resulting in an estimated NOAEL and LOAEL of 1.1 and 3.2 mg/kg BW/d, respectively.

White and Finley (1978) and White *et al. (*1978) demonstrated adverse effects on reproductive capacity in both male and female mallards exposed to cadmium. White and Finley (1978), in the study described above, noted decreased egg production in mallards fed 200 mg/kg cadmium in diet (20.0 mg/kg BW/d). At 200 mg/kg (20.0 mg/kg BW/d) in diet for 90 days, male mallard testes weighed significantly less than control birds. In addition, the authors considered the three treatment groups (2, 20, and 200 mg/kg cadmium in diet) to have significantly decreased testes weight 30 days post-treatment compared to controls. However, since control birds were not sacrificed at the same time point (30 days post-treatment) and random samples of controls at other time points were used for comparison, these data were not used directly. The testes of three of five male mallards at 200 mg/kg (20.0 mg/kg BW/d) had severe aspermatogenesis and were atrophied (White *et al.*1978). No significant pathological alterations were present in testes of control ducks whereas some birds fed 20 mg/kg cadmium (1.45 mg/kg BW/d) had few primary spermatocytes, but no mature spermatozoa.

IDENTIFICATION OF THE MOST SENSITIVE, ECOLOGICALLY RELEVANT LOAEL

In order to help interpret estimated doses between the updated TRV-low (0.7 mg/kg BW/d) and the original TRV-high (10.43 mg/kg BW/d), the most sensitive, ecologically relevant LOAEL for cadmium exposure in birds was determined based on the review of endpoints, studies, and effects above. A LOAEL of 1.0 mg/kg BW/d was identified based on kidney effects in mallards from Cain *et al*. (1983). This LOAEL is supported by other studies identifying potential reproductive effects near this dose, such as White *et al*. (1978) and Leach *et al*. (1979). Furthermore, the narrow range between the NOAELs and LOAELs overall and the selected TRV-low and TRV-high reinforces the apparent steepness of the dose-response curve, particularly for reproductive and renal endpoints.

INDICATORS OF EXPOSURE

While tissue concentrations in and of themselves cannot be considered an effect of cadmium exposure, they do appear to correlate with diets that contain cadmium and are potentially a strong indicator of cadmium exposure in field-collected organisms. The reviews by Eisler (2000), Furness (1996), and Scheuhammer (1987) identified potential criteria for tissue concentrations. However, such tissue concentration criteria may not be applicable to pelagic seabirds, for which consistently higher tissue concentrations have been measured even in supposedly unpolluted areas (Furness, 1996).

Most of the studies reviewed included information on changes in cadmium levels in various tissues that varied with the levels of cadmium in diet. In particular, kidney and liver tissue cadmium concentrations generally show consistent increases with dietary cadmium concentrations. A few studies described a perceived connection between some attribute of the organism (Mayack *et al.*1981; Bokori *et al.*1996) or other components of the diet, such as protein levels and various metals, which influence cadmium tissue concentrations (see Body Weight discussion).

Mayack *et al. (*1981), in the studies described above, saw significant differences in cadmium tissue residue levels between treatment groups for kidney, liver, and feathers. Elevated tissue concentrations followed a step-wise dose-response with the highest tissue concentrations in the 100 mg/kg group (209 and 132 mg/kg wet weight for liver and kidney, respectively) and decreasing tissue concentrations with decreasing dietary exposure for both protein levels. An interaction between cadmium and protein levels in the diet with kidney cadmium concentrations was statistically significant. With the exception of three samples, blood, muscle, and brain tissues all had cadmium residues below the respective method detection limits. The exceptions, each from a different bird and tissue, were from the 18% protein, 100 mg/kg cadmium treatment group. Although cadmium levels in liver and kidney were low in wood ducks receiving 10 mg/kg cadmium in diet after 12 weeks, the levels were higher than mallards exposed to dietary concentrations two times higher for the same time period (White and Finley 1978). Mayack *et al*. (1981) also hypothesized that liver to kidney ratios of cadmium exceeding

one indicate that renal damage has occurred and that these ratios may be useful in determining cadmium intoxication in waterfowl.

Bokori *et al*. (1996), in the study described above, reported tissue cadmium concentrations increased in direct proportion to exposure, usually by one (kidney, skeletal muscles, brain) or two orders of magnitude (myocardium, liver, lungs). The highest increase (620-fold) of cadmium in tissues of birds treated with 75 mg/kg cadmium relative to tissues of control birds was for the spleen. For the 75 mg/kg cadmium group, the highest tissue concentration was found in the kidney and liver, up to averages of 724 and 579 mg/kg, dry weight respectively. The authors noted that, as supported by earlier studies, the accumulation of cadmium in tissues increases in proportion to the cadmium concentration in diet and the duration of the study.

Leach *et al*. (1979), in the studies described above, found that cadmium in the diet resulted in significant increases in liver and kidney concentrations and small increases in skeletal muscle. The kidney accumulated the most cadmium with significant increases with all three treatments (averages of 274, 708, and 541 mg/kg dry, fat-free basis, respectively for Experiment 3). The liver accumulated substantial amounts of cadmium at the 12 (Experiment 2 only) and 48 mg/kg levels. While muscle tissue showed a more limited ability to accumulate cadmium, the two higher levels (12 and 48 mg/kg) did result in significant increases in tissue content. The authors also noted that chicks killed at 2 weeks of age had tissue levels of cadmium approximately one-half of those found in chicks at 6 weeks of age. The four-week-old chicks were intermediate between the other two. The investigators also found that 48 mg/kg cadmium in the diet of chickens resulted in increased concentrations of cadmium in the egg compared with eggs of birds with the 3 and 12 mg/kg diets, but not compared to the control group. Shorter-term experiments showed no significant increases in cadmium levels in the egg. This result may indicate that even very low levels of cadmium in diet can result in detectable cadmium levels in the egg over the long term, and suggests that attention should be paid to the levels of cadmium in standard feed for the laying hen.

Cain *et al. (*1983), in the study described above, saw significantly higher liver concentrations at 12 weeks of age with increased dietary cadmium levels and exposure duration. At 12 weeks, the cadmium concentration in liver tissue was twice that in diet (i.e., 42.2 mg/kg wet weight liver for 20 mg/kg cadmium in the diet). However, the bone concentrations showed a different trend with femur concentration in all 12 week-old ducklings declining from the values detected at 4 and 8 weeks of age. The authors had no explanation but did refer to the Mayack *et al*. (1981) study where increasing amounts of cadmium were fed to wood ducks and feathers were observed to accumulate cadmium. They suggested that cadmium is incorporated into the feather structure during feather development and cadmium may be mobilized from the bone as a result. This hypothesis suggests the need to study the possible correlation between feather development and reduced femur cadmium.

White and Finley (1978), in the study described above, reported livers and kidneys accumulated the highest tissue concentrations, particularly for birds treated with 200 mg/kg dietary cadmium. At 60 days, liver and kidney tissue concentrations for the 200

mg/kg cadmium group averaged 109.6 and 134.2 mg/kg wet weight, respectively. Kidney lesions were related to the concentration of dietary cadmium and to the period of treatment. Egg cadmium concentrations were increased significantly for birds fed 20 and 200 mg/kg cadmium in the diet.

Overall, tissue concentrations are generally related to cadmium exposure, particularly for liver and kidney. Liver and kidney concentrations in the highest dietary treatment groups of some of the reviewed studies (e.g., Cain *et al*., 1983; White and Finley, 1978; Mayack *et al*., 1981) were at or above the "adverse effects expected" liver and kidney tissue criteria of 40 and 100 mg/kg fresh weight, respectively (Furness, 1996). Direct comparisons to the liver and kidney tissue concentrations in Leach *et al. (*1979), which were reported on a dry weight, fat-free basis, and in Bokori *et al. (*1996), which were in dry weight, were not possible. Egg and bone concentrations may be affected by confounding factors, such as cadmium mobilization from bone during feather development (Mayack *et al*., 1981).

CONSIDERATION OF BIOAVAILABILITY/BIOACCESSIBILITY OF CADMIUM

Hazardous waste sites and permitted facilities frequently include cadmium as a contaminant of potential ecological concern (COPEC). Cadmium can be found in the environment in many different forms (e.g., cadmium carbonate and cadmium phosphate) with varying degrees of bioavailability/bioaccessibility. However, the selected cadmium TRV-Low is based on cadmium chloride, a soluble and bioavailable form of cadmium. When the NOAEL TRV is applied in the Phase 1 Predictive Assessment using conservative exposure assumptions (e.g., high site fidelity and/or intake rates), back-calculated soil concentrations at or approaching ambient or background conditions may appear to pose risk. Therefore, if cadmium has hazard quotients above one during the screening level ecological risk assessment using the updated avian TRV-Low, the form(s) of cadmium present on site and their bioavailability or bioaccessibility relative to cadmium chloride should be determined. Examples of studies measuring *in vitro* and *in vivo* cadmium bioavailability and bioaccessibility include Schroder *et al.* (2003) and Chan *et al.* (2007). Please see EcoNOTE 4 (DTSC, HERD, 2000) for further information. Implementation of the refined exposure assessment and subsequent risk characterization can follow the Data Quality Objectives (DQO) process outlined by the USEPA (1993).

CONCLUSIONS AND RECOMMENDATIONS

The BTAG has updated the current avian BTAG TRV for cadmium, as summarized in Table 3. After consideration of the endpoints, dosing information, evaluation of the experimental results, and limitations of the experiments, the BTAG recommends an avian cadmium NOAEL (TRV-Low) of 0.7 mg/kg BW/day, which is based primarily on the kidney toxicity data contained in Mayack *et al*. (1981). This conclusion is supported by at least five other studies suggesting that a 0.7 mg/kg BW/day cadmium dose would be protective of reproductive, growth, and renal effects seen at doses within one order of magnitude. In addition, the most sensitive, ecologically relevant LOAEL was identified as 1.0 mg/kg/d based on kidney nephrosis in mallards (Cain *et al*., 1983). The

decision to alter the BTAG TRV is based on the best available data developed after the initial determination of the BTAG avian TRV-Low in 1997. As new information becomes available, this TRV, or others may be revised. The BTAG will not consider revising any TRV without sufficient scientific justification and documentation, as documented in this and previous EcoNOTEs on TRV derivation.

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Table 1. Avian Toxicity Data for Cadmium Reported in EPA Eco-SSL (March 2005) with Updates.

Eco-SSL Result #	Eco-SSL Ref #	Reference	Chemical Form	Test Species	Exposure Duration	Age	General Effect Group	Effect Type	Effect Measure	Response Site	Study NOAEC (mg/kg or mg/L)	Study LOAEC (mg/kg or mg/L)	Conc Units	Body Weight Reported?	Body Weight in kg	Ingestion Rate Reported?	Ingestion Rate in kg/day or L/day (Reported or Nagy 1987 - all bird)	Ingestion Rate in kg/day or L/day (Nagy 2001 - all bird)	ECOSSL NOAEL Dose (mg/kg/day)	ECOSSL LOAEL Dose (mg/kg/day)	Rev. NOAEL Dose (mg/kg/day)	Rev. LOAEL Dose (mg/kg/day)
54	400	Jacobs et al, 1978	$CdCl_2$	Japanese Quail	7 d	7 d	GRO	GRO	BDWT	WO	1.0		mg/kg FD	Y	0.042	Y	0.0052		0.125		0.12	
94	400	Jacobs et al, 1978	$CdCl_2$	Japanese Quail	7 d	7 d	BEH	FDB	FCNS	WO	1.0		mg/kg FD	Y	0.042	Y	0.0052		0.125		0.12	
44	398	Leach et al, 1979	$CdSO_4$	Chicken	12 w	8 mo	REP	REP	EGPN	WO	3.0	12.0	mg/kg FD	N	1.6	N	0.079	0.10	0.148	0.59	0.19	0.75
55	356	Stoewsand et al 1986	Unknown	Japanese Quail	63 d	1 d	GRO	GRO	BDWT	WO	2.00		mg/kg FD	N	0.14	N	0.013	0.018	0.260		0.27	
NA	NEW	Teshfam.et al., 2006	$CdCl_2$	Chicken	48 d	1 d	GRO	GRO	BDWT	WO	5.0	50.0	mg/kg FD	Y	2.04	N	0.092	0.12	0.23	2.27	0.29	2.89
25	393	Mayack et al, 1981	$CdCl_2$	Wood duck	12 w	1 w	PTH	HIS	GHIS	KI	7.61	77.85	mg/kg FD	Y	0.51	N	0.038	0.046	0.559	5.72	0.68	6.96
26	392	Lefevre et al, 1982	$CdCl_2$	Chicken	5 w	1 d	PTH	ORW	ORWT	LU	10.0	100	mg/kg FD	Y	0.28	Y	0.020		0.708	7.08	0.71	7.08
56	392	Lefevre et al, 1982	$CdCl_2$	Chicken	5 w	1 d	GRO	GRO	BDWT	WO	10.0	100	mg/kg FD	Y	0.28	Y	0.020		0.708	7.08	0.71	7.08
45	398	Leach et al, 1979	$CdSO_4$	Chicken	12 mo	6 mo	REP	REP	EGPN	WO	12.0	48.0	mg/kg FD	N	1.6	N	0.079	0.10	0.593	2.37	0.75	3.00
57	398	Leach et al, 1979	$CdSO_4$	Chicken	6 w	1 d	GRO	GRO	BDWT	WO	12.0	48.0	mg/kg FD	Y	0.62	N	0.043	0.052	0.826	3.30	1.01	4.04
1	366	Cain et al, 1983	$CdCl_2$	Mallard Duck	12 w	1 d	BIO	CHM	HMGL	BL	14.6		mg/kg FD	Y	1.13	N	0.063	0.079	0.858		1.02	
58	366	Cain et al, 1983	$CdCl_2$	Mallard Duck	12 w	1 d	GRO	GRO	BDWT	WO	14.6		mg/kg FD	Y	1.13	N	0.063	0.079	0.858		1.02	
28	366	Cain et al, 1983	$CdCl_2$	Mallard Duck	12 w	1 d	PTH	ORW	ORWT	LI	14.6		mg/kg FD	Y	1.13	N	0.063	0.079	0.858		1.02	
27	375	Bokori et al, 1996	$CdSO_4$	Chicken	39 w	14 d	PTH	ORW	SMIX	LI	25.0	75.0	mg/kg FD	Y	5.58	N	0.18	0.24	0.799	2.40	1.05	3.16
46	375	Bokori et al, 1996	$CdSO_4$	Chicken	39 w	14 d	REP	REP	TEWT	TE	25.0	75.0	mg/kg FD	Y	5.58	N	0.18	0.24	0.799	2.40	1.05	3.16
2	386	Blalock and Hill, 1988	$CdSO_4$	Chicken	2 w	1 d	BIO	CHM	HMGL	BL	10.0	20.0	mg/kg FD	Y	0.16	N	0.020	0.021	1.02	2.04	1.28	2.56
29	396	White and Finley, 1978	$CdCl_2$	Mallard Duck	90 d	1 yr	PTH	ORW	ORWT	KI	15.2	210	mg/kg FD	Y	1.15	Y	0.11		1.22	16.9	1.45	20.03
31	399	White et al 1978	$CdCl_2$	Mallard	60 d	1 yr	PTH	ORW	SMIX	KI	15.2	210	mg/kg FD	Y	1.15	Y	0.11		1.53	21.1	1.45	20.03
59	1369	Hill, 1974	$CdSO_4$	Chicken	2 w	1 d	GRO	GRO	BDWT	WO	14.6		mg/kg FD	N	0.33	N	0.028	0.034	1.25		1.50	
24	375	Bokori et al, 1996	$CdSO_4$	Chicken	5 w	14 d	PHY	PHY	FDCV	WO	25.0	75.0	mg/kg FD	Y	1.59	N	0.079	0.099	1.24	3.71	1.56	4.69
3	433	Pilastro et al, 1993	$CdCl_2$	Starling	22 w	NR	BIO	ENZ	CYTC	LI	10.0	50.0	mg/kg FD	Y	0.074	N	0.011	0.012	1.44	7.21	1.64	8.22
30	433	Pilastro et al, 1993	$CdCl_2$	Starling	22 w	NR	PTH	ORW	SMIX	LI	10.0	50.0	mg/kg FD	Y	0.074	N	0.011	0.012	1.44	7.21	1.64	8.22
18	410	Silver & Nudds, 1995	$CdCl_2$	Black duck	106 d	NR	BEH	BEH	ACTV	WO		6.53	mg/kg FD	N	1.4	Y	0.057			0.265		0.27
19	392	Lefevre et al, 1982	$CdCl_2$	Chicken	5 w	1 d	BEH	FDB	FCNS	WO		10.0	mg/kg FD	Y	0.28	Y	0.020			0.708		0.71
35	366	Cain et al, 1983	$CdCl_2$	Mallard Duck	12 w	1 d	PTH	HIS	NPHR	KI		14.6	mg/kg FD	Y	1.13	N	0.063	0.079		0.858		1.02
20	5265	Fadil and Magid, 1996	$CdCl_2$	Chicken	30 d	1 d	BEH	FDB	WCON	WO		10.0	mg/L DR	N	0.040	N	0.0068	0.0079		1.05		2.00
68	5265	Fadil and Magid, 1996	$CdCl_2$	Chicken	30 d	1 d	GRO	GRO	BDWT	WO		10.0	mg/L DR	N	0.040	N	0.0068	0.0079		1.05		2.00
100	5265	Fadil and Magid, 1996	$CdCl_2$	Chicken	30 d	1 d	BIO	CHM	RBCE	BL		10.0	mg/L DR	N	0.040	N	0.0068	0.0079		1.05		2.00

Note: Revised dose calculations used Nagy et al. (2001) allometric ingestion rate calculations rather than Nagy et al. (1987) equations for studies in which ingestion rate was not directly reported.

Abbreviations: ACTV = general activity levels; BDWT = body weight changes; BEH = behavior; BL = blood; CHM = chemical changes; CYTC = NADPH cytochrome C reductase; d = days; DR = Drinking water; EGPN = egg production; FFCNS = food consumption; FD = food; FDB = feeding behavior; FDCV =food conversion efficiency; GCHM = general biochemical; GHIS = general histology; GRO = growth; GLSN = gross lesions; GRS = gross wasting; HE = heart; HIS = histology; HMCT = hematocrit; HMGL = hemoglobin; IN = intestine; KI = kidney; LI = liver; LOAEL = lowest observed adverse effect level; LU= lung; M = measured; m = months; MOR = mortality, MORT = mortality; MU = multiple; NCRO = necrosis; NOAEL = no observed adverse effect level; NPHR = nephrosis; NR = Not reported; OR = other oral; ORW = organ weight changes; PHY = physiology; PROG = progeny counts; REP = reproduction; SMIX = weight relative to body weight; SURV = survival; w = weeks; WO = whole organism

Table 2. Literature Summary

Reference	Test Species	Exposure Duration	Age	Effect Group	Effect Measure	NOAEL Dose (mg/kg/day)	LOAEL Dose (mg/kg/day)	Conclusion
Jacobs et al, 1978	Japanese Quail	7 d	7 d	Growth	Body Weight	0.1		
Jacobs et al, 1978	Japanese Quail	7 d	7 d	Behavior	Food Consumption	0.1		
Leach et al, 1979	Chicken	12 w	8 mo	Reproduction	Egg Production	0.2	0.8	Retain
Teshfam.et al., 2006	Chicken	48 d	1 d	Growth	Body Weight	0.3	2.9	
Stoewsand et al 1986	Japanese Quail	63 d	1 d	Growth	Body Weight	0.3		
Mayack et al, 1981	Wood duck	12 w	1 w	Pathology	Kidney Histology	0.7	7.0	Retain
Lefevre et al, 1982	Chicken	5 w	1 d	Pathology	Lung Weight	0.7	7.1	
Lefevre et al, 1982	Chicken	5 w	1 d	Growth	Body Weight	0.7	7.1	
Leach et al, 1979	Chicken	12 mo	6 mo	Reproduction	Egg Production	0.8	3.0	Retain
Leach et al, 1979	Chicken	6 w	1 d	Growth	Body Weight	1.0	4.0	Retain
Cain et al, 1983	Mallard Duck	12 w	1 d	Biochemical	Hemoglobin	1.0		Retain
Cain et al, 1983	Mallard Duck	12 w	1 d	Growth	Body Weight	1.0		Retain
Cain et al, 1983	Mallard Duck	12 w	1 d	Pathology	Liver Weight	1.0		Retain
Bokori et al, 1996	Chicken	39 w	14 d	Pathology	Relative Liver Weight	1.1	3.2	Retain
Bokori et al, 1996	Chicken	39 w	14 d	Reproduction	Testes Weight	1.1	3.2	Retain
White and Finley, 1978	Mallard Duck	90 d	1 yr	Pathology	Kidney Weight	1.2	16.0	Retain
Blalock and Hill, 1988	Chicken	2 w	1 d	Biochemical	Hemoglobin	1.3	2.6	
Hill, 1974	Chicken	2 w	1 d	Growth	Body Weight	1.5		
White et al 1978	Mallard	60 d	1 yr	Pathology	Relative Kidney Weight	1.5	20.0	Retain
Bokori et al, 1996	Chicken	5 w	14 d	Physiological	Food Conversion Efficiency	1.6	4.7	Retain
Pilastro et al, 1993	Starling	22 w	NR	Biochemical	Liver NADPH cytochrome C reductase activity	1.6	8.2	
Pilastro et al, 1993	Starling	22 w	NR	Pathology	Relative Liver Weight	1.6	8.2	
Silver and Nudds, 1995	American black duck	106 d	NR	Behavior	general activity levels		0.3	
Lefevre et al, 1982	Chicken	5 w	1 d	Behavior	Food Consumption		0.7	
Cain et al, 1983	Mallard Duck	12 w	1 d	Pathology	Kidney Nephrosis		1.0	Retain
Fadil and Magid, 1996	Chicken	30 d	1 d	Behavior	Food Consumption		2.0	
Fadil and Magid, 1996	Chicken	30 d	1 d	Growth	Body Weight		2.0	
Fadil and Magid, 1996	Chicken	30 d	1 d	Biochemical	Red Blood Cell		2.0	

Table 3. Summary of previous and proposed avian TRVs for cadmium.

TRV	Dose (mg/kg BW/d)	Endpoint	Study
Original BTAG NOAEL / TRV-low	0.08	Kidney histology in mallards with uncertainty factor of 10	Cain et al., 1983
Updated BTAG NOAEL / TRV-low	0.7	Kidney histology in wood ducks	Mayack et al., 1981
New BTAG LOAEL	1.0	Kidney histology in mallards	Cain et al., 1983
Eco-SSL geomean NOAEL	1.47	Geometric mean of growth and reproduction	EPA, 2005
BTAG mid-range effect level / TRV-high	10.43	decreased body weight and testes weight in Japanese quail	Richardson and Spivey Fox 1974

Figure 1. Cadmium TRVs for Oral Exposure to Birds based on NOAELs and LOAELs (Y axis logarithmic scale)